Management of multiple myeloma

Recent advances have resulted in improved treatment options and remission rates, writes Mary Kelly

MULTIPLE myeloma (MM) is a cancer of the plasma cells in the bone marrow (BM). MM is the second most common haematological cancer after lymphoma. The cause of MM is unknown, risk factors include age, radiation, agricultural exposures and familial risk. Age at diagnosis varies; the majority are over 50 years, with higher male predominance. MM occurs in all races, incidence is higher among black populations. In Ireland 222 patients are diagnosed each year.1

Recent advances in our understanding of the pathophysiology of MM have resulted in improved treatment options, remission rates and importantly, disease free survival. Treatments to halt MM and improvement in supportive therapies have improved quality of life (QOL). However MM remains incurable. This article provides an overview of MM diagnosis and management.

Pathophysiology

MM occurs due to unregulated, proliferation of neoplastic monoclonal plasma cells that accumulate in the marrow. B-cell lymphocytes mature into plasma cells in response to infection. Plasma cells produce and release proteins called immunoglobulins (antibodies) which attack and help kill disease-causing organisms. Each immunoglobulin (see Figure 1) molecule consists of two light chains known as kappa and lambda and two heavy chains defined as five classes of immunoglobulins: IgG, IgA, IgM, IgD and IgE.2

MM is characterised by abnormal overproduction of one of these immunoglobulins by the malignant clones.3 This overproduced protein is known as the monoclonal (M) protein. Normally mature plasma cells occupy < 5% of the bone marrow (BM), however in myeloma, there are > 10% mature plasma cells in the BM.4

Clinical features

MM is often asymptomatic, 30% of new MM cases are diagnosed incidentally. However patients can present with anaemia, hypercalcaemia, elevated erythrocyte sedimentation rate (ESR), renal dysfunction, plasma hyperviscosity or bleeding problems. These findings may be treated as separate medical conditions if MM is not included in the differential diagnosis, often leading to delayed referral, diagnosis and poor symptom control.5

MM is defined by the presence of end organ damage (CRAB: Hypercalcaemia, renal insufficiency, anaemia and bone lesions). In most patients there is a constellation of clinical, laboratory, radiological and pathological findings.6 It is important to distinguish other M protein conditions; monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM). Clinically, MGUS has a monoclonal protein without presence of CRAB and with < 10% plasma cells in the BM. MGUS patients have a 1% per year risk of progression and require three to six monthly review.6 SMM defined as M-Protein > 30g/dL and/or 10% or more plasma cells in BM, and an absence CRAB features. SMM has a higher risk of progression to myeloma (10% per year – first five years), these patients can be observed for years before any active treatment is required.

Bone disease

Bone destruction is a hallmark of MM. Up to 90% of patients develop bone lesions (see Figure 2).7 MM patients develop skeletal complications including severe bone pain, hypercalcaemia, pathologic fractures and spinal cord compression.
Anaemia occurs in 80% of patients. Symptoms include fatigue, weakness and dyspnoea. Prompt treatment is important to improve patients’ quality of life. Treatment includes blood transfusions and treatment of myeloma. Erythropoietin is given to patients whose anaemia persists after starting treatment.8

Infections

Recurrent infections are common. Many patients die as a result of bacterial infections.15 Therefore patient education, prompt recognition of infection and immediate intervention is essential. Patients receive prophylactic antibiotics where the treatment regime is considered high risk, eg. ASCT. Vaccinations for influenza and pneumonia are recommended. Herpes Zoster is common and requires antiviral therapy. Finally, patients with hypogammaglobulinaemia and recurrent infections benefit from monthly IV immunoglobulin.

Renal insufficiency

Renal insufficiency is found in 24% of patients and is associated with a poorer prognosis.6 However, if successfully treated prognosis improves. Fluid hydration of 3L daily is recommended throughout the disease course and improves overall survival. Management is multi-focused including adequate hydration, anti-myeloma therapy, prompt management of hypercalcaemia, dose adjustment of bisphosphonate therapy, avoidance of nephrotoxic drugs, eg. NSAIDs, contrast media and prompt treatment of infections.

In addition, patient education on preventative measures is crucial to preserve kidney function.

Hypercalcaemia

Hypercalcaemia occurs in 13% of patients. Early recognition of signs and symptoms including nausea, vomiting, lethargy and confusion is essential to initiate prompt intervention including IV fluids, bisphosphonates and steroids.

The gastrointestinal symptom can be mistakenly attributed to the underlying disease, cytotoxic or radiation therapy. Hypercalcaemia is reversible with appropriate treatment and its progression can often be prevented. However, left untreated hypercalcaemia leads to renal failure, progression of neurological symptoms, cardiac arrest or coma.2

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Diagnosis and treatment

The diagnosis of MM is based on the demonstration of a M protein in serum or urine and/or lytic lesions by radiography, and the presence of more than 10% plasma cells in the BM. Diagnostic investigations are outlined in Table 1. Of patients 1-2% will have ‘non secretory myeloma’, whereby no M protein is detected.

Patients with asymptomatic disease require no treatment and are monitored for disease progression. Eradication of myeloma is rare. However the availability of effective new drugs to treat myeloma has significantly extended survival and quality of life.

The goals of myeloma treatment are:

Facilitate fast control of the disease and reverse any myeloma-related complications (CRAB)

Well-tolerated treatment, minimal side effects

Decrease the risk of early morbidity

Allow successful harvesting of stem cells when autologous stem cell transplant (ASCT) is a treatment option.15

Patients are divided into two groups at diagnosis:

Those who are elderly/medically compromised and unsuitable for ASCT.

In the transplant-eligible population, randomised trials have demonstrated improved outcomes with the use of maintenance therapy with thalidomide, and, more recently the use of induction therapy that includes novel agents, particularly bortezomib.15 Treatment choice is influenced by several factors including oral versus IV therapy, renal impairment and risk factors, eg. thromboembolism.

Table 2 outlines the drugs commonly used in MM and their associated side effects. Bortezomib and thalidomide are associated with peripheral neuropathy, careful assessment is required and treatment includes dose reduction and pain control. Thalidomide and lenalidomide increase thromboembolism risk, patients require prophylaxis unless contraindicated.14 Due to the potential teratogenicity of these drugs, patients are educated regarding contraceptive advice and avoiding pregnancy, risk management programmes are in place.

Following induction therapy haematopoietic stem cells are collected, the patient receives high dose melphalan and ASCT, mortality risk is 1%. ASCT is not curative, median duration of response is two years.7 Patients with complete response (CR) and very good partial response (VGPR) require close follow up. However if CR/VGPR is not achieved a second ASCT or maintenance therapy until progression may be of benefit.3

For patients ineligible for transplant, the addition of novel agents to the former melphalan and prednisolone (MP) regimen has produced higher remission rates, longer progression free survival (PFS) and, in some trials, longer overall survival. This approach does increase the risk of toxicities. Lenalidomide and weekly dexamethasone is a well tolerated alternative regime. Both strategies induce remissions in approximately 70% of patients.15

Relapsed/refractory myeloma

In the majority of patients, MM will relapse. Re-treatment is individualised based on age, presence of comorbidities, previous therapy, quality and duration of response and toxicities and tolerance to therapy. Unfortunately, the duration of response to treatment tends to decrease with each successive relapse.

Bisphosphonates

Bisphosphonates given monthly IV are
Within the oral cavity. Dental assessment phonates characterised by exposed bone—a complication associated with bisphosphonate therapy. Osteonecrosis of the jaw (ONJ) is reduced where indicated to preserve renal effects of bisphosphonate where possible. ONJ guidelines and treatment is completed pre bisphosphonate where possible. ONJ guidelines have been developed to promote prevention, early detection and minimise the effects of ONJ.

Supportive care
Supportive care is an important component of MM management, provided concurrently with treatment. Transfusion support, G-CSF and erythropoietin therapies have lead to improved QOL and prolonged survival. Unrelieved pain is recognised to be a source of distress and psychological symptoms. Nurses have a key role in pain assessment and evaluation of interventions including: analgesia, radiotherapy and bisphosphonates. Early collaboration with palliative care is essential.

Studies on the lived experience of myeloma highlight patient’s challenges include, living with an ‘unknown cancer’, isolation and fear of recurrence. In response an annual National Myeloma week in June raises awareness and understanding of this incurable cancer. In addition, support is available from www.mymyeloma.ie (dedicated patient website), support groups, Irish Cancer Society and Myeloma UK.

Myeloma remains a complex disease to diagnose and treat. Education about the potential complications of MM and early intervention is fundamental to patient outcome. Treatment options have significantly improved over the past decade along with supportive therapies resulting in improved quality and survival. Nurses must remain abreast of new developments in order to promote excellence in care.

Table 1

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<tr>
<th>Diagnostic investigations for multiple myeloma</th>
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<tbody>
<tr>
<td><strong>Peripheral bloods</strong></td>
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<tr>
<td>• Full blood count (FBC)/Blood film</td>
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<tr>
<td>• Full biochemistry (including urea and creatinine, calcium and LDH)</td>
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<tr>
<td>• ESR</td>
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<tr>
<td>• Serum protein electrophoresis and quantitative immunoglobulin</td>
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<td>• Beta 2microglobulin</td>
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<td>• Serum free light chain assay</td>
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<td>• C reactive protein</td>
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<tr>
<td><strong>Radiology</strong></td>
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<tr>
<td>• Skeletal survey</td>
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<tr>
<td><strong>24-hour urine collection</strong></td>
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<tr>
<td>• For total protein and Bence Jones Protein (BJP)</td>
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<tr>
<td>• Immunofixation</td>
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<tr>
<td><strong>Bone marrow</strong></td>
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<tr>
<td>• Aspirate/Biopsy/Cytogenetics (where available)/Fluorescent in situ Hybridization (FISH)</td>
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<tr>
<td><strong>Selected others</strong></td>
</tr>
<tr>
<td>• Solitary lytic lesion biopsy</td>
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<td>• Plasma viscosity</td>
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<td>• MRI</td>
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<td>• Abdominal fat/rectal biopsy if amyloidosis suspected</td>
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References
1. Irish Cancer Society. Understanding Myeloma. ICS patient information booklet, 2010